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(54) Title: THERAPEUTIC AGENTS

(57) Abstract: Compounds of formula (I), processes for preparing such compounds, their use in the treatment of obesity, psychiatric disorders, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders and to pharmaceutical compositions containing them.

WO 2007/011285 A1

THERAPEUTIC AGENTS

Field of invention

The present invention relates to certain compounds of formula I, to processes for preparing
5 such compounds, to their use in the treatment of obesity, psychiatric and neurological
disorders, and to pharmaceutical compositions containing them.

Background of the invention

Melanin concentrating hormone (MCH) is a cyclic peptide that was first isolated from fish
10 over 15 years ago. In mammals, MCH gene expression is localised to the ventral aspect of
the zona inserta and the lateral hypothalamic area (Breton et al., *Molecular and Cellular
Neurosciences*, vol. 4, 271-284 (1993)). The latter region of the brain is associated with the
control of behaviours such as eating and drinking, with arousal and with motor activity
(Baker, B., *Trends Endocrinol. Metab.* 5: 120-126(1994), vol. 5, No. 3, 120-126 (1994)).
15 Although the biological activity in mammals has not been fully defined, recent work has
indicated that MCH promotes eating and weight gain (US 5,849,708). Thus, MCH and its
agonists have been proposed as treatments for anorexia nervosa and weight loss due to
AIDS, renal disease, or chemotherapy. Similarly, antagonists of MCH can be used as a
treatment for obesity and other disorders characterised by compulsive eating and excessive
20 body weight. MCH projections are found throughout the brain, including the spinal cord,
an area important in processing nociception, indicates that agents acting through MCH1r,
such as compounds of formula I, will be useful in treating pain.

Two receptors for MCH (MCH receptor 1 (MCH1r) (Shimomura et al. *Biochem Biophys
25 Res Commun* 1999 Aug 11;261(3):622-6) & MCH receptor 2 (MCH2r) (Hilol et al. *J Biol
Chem.* 2001 Jun 8;276(23):20125-9)) have been identified in humans, while only one
(MCH1r) is present in rodent species (Tan et al. *Genomics* 2002 Jun;79(6):785-92). In
mice lacking MCHr1, there is no increased feeding response to MCH, and a lean
phenotype is seen, suggesting that this receptor is responsible for mediating the feeding
30 effect of MCH (Marsh et al. *Proc. Natl. Acad. Sci. USA*, 2002 Mar 5;99(5):3240-5). In
addition, MCHr1 antagonists have been demonstrated to block the feeding effects of MCH

(Takekawa et al. *Eur. J. Pharmacol.* 2002 Mar 8;438(3):129-35), and to reduce body weight & adiposity in diet-induced obese rats (Borowsky et al. *Nature Med.* 2002 Aug;8(8):825-30). The conservation of distribution and sequence of MCHr1 suggest a similar role for this receptor in man and rodent species. Hence, MCHr1 antagonists have
5 been proposed as a treatment for obesity and other disorders characterised by excessive eating and body weight.

WO 2004/092181 discloses heterocyclic compounds, which are antagonists to the MCHr1.

10 There is an unmet need for MCHr1 antagonists that are more potent, more selective, more bioavailable and produce less side effects than known compounds in this field.

Summary of the invention

It is an object of the present invention to provide compounds, which are useful in treating
15 obesity and related disorders, psychiatric disorders, neurological disorders and pain. This object has been reached in that a compound of formula I have been provided for use as a MCHr1 antagonist.

According to another aspect of the invention a pharmaceutical formulation is provided
20 comprising a compound of formula I, and a pharmaceutically acceptable adjuvant, diluent or carrier.

According to a further aspect of the invention, the use of a compound of formula I is provided, in the preparation of a medicament for the treatment or prophylaxis of conditions
25 associated with obesity.

According to yet another aspect of the invention, a method is provided of treating obesity, psychiatric disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related
30 conditions, and neurological disorders and pain related disorders, comprising administering

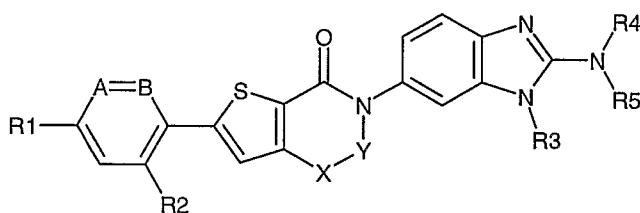
a pharmacologically effective amount of a compound of Formula I to a patient in need thereof.

According to another aspect of the invention, a process for the preparation of compounds
5 of formula I is provided.

According to a further aspect of the invention, a method is provided of treating obesity,
type II diabetes, Metabolic syndrome and prevention of type II diabetes comprising
administering a pharmacologically effective amount of a compound of formula I to a
10 patient in need thereof.

Description of the invention

The invention relates to compounds of the general formula (I)



15

(I)

wherein

A and B independently represent C or N,

X-Y represents C=N, or;

X represents NH and Y represents C=O, or;

20 X-Y represents N=N,

R¹ and R² independently represent H, C₁₋₃ alkyl (optionally substituted with one or more F), C₁₋₃ alkoxy (optionally substituted with one or more F), Cl or F,

R³ represents H, C₁₋₃ alkyl (optionally substituted with a hydroxy, methoxy, amino, methylamino, dimethylamino, pyrrolidinyl or morpholinyl group),

25 R⁴ and R⁵ independently represent H, C₁₋₃ alkyl (optionally substituted with a hydroxy, methoxy, amino, methylamino, dimethylamino, pyrrolidinyl or morpholinyl), or;

R⁴ and R⁵ are joined to form, together with the nitrogen atom to which they are attached, a pyrrolidine, piperidine, piperazine or morpholine ring (optionally substituted with hydroxy,

oxo, C₁₋₃ alkyl (optionally substituted with hydroxy, methoxy or dimethylamino) or with a C₁₋₃ alkoxy group (optionally substituted with hydroxy, methoxy or dimethylamino)), and tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

5

Particular groups now follow in which some of A, B, X, Y, R¹, R², R³, R⁴ and R⁵ in compounds of formula I are further defined. It will be understood that such group definitions may be used where appropriate with any of the other group definitions, claims or embodiments defined hereinbefore or hereinafter.

10

In a particular group of compounds of formula I,

A and B both represent C, and

X-Y represents C=N, or

X-Y represents N=N.

15

In another particular group of compounds of formula I,

A and B both represent C, and

X-Y represents N=N.

20

In a further group of compounds of formula I,

A and B both represent C,

X-Y represents N=N,

R¹ represents Cl, F, CF₃, CHF₂, CH₂F, methyl, OCF₃ or OCHF₂,

R² represents H, Cl, F or CH₃,

25

R³ represents methyl, ethyl, iso-propyl, hydroxyethyl or dimethylaminoethyl,

R⁴ and R⁵ independently represent H, methyl, hydroxyethyl or dimethylaminoethyl, or;

R⁴ and R⁵ are joined to form, together with the nitrogen atom to which they are attached, a pyrrolidine, piperidine, piperazine or morpholine ring.

30

The term "pharmaceutically acceptable salt" refers to pharmaceutically acceptable acid addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is,

for example, an acid-addition salt of a compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as:

(1S)-(+)-10-camphorsulfonic acid; cyclohexylsulfamic acid; phosphoric acid; dimethylphosphoric acid; p-toluenesulfonic acid; L-lysine; L-lysine hydrochloride; 5 saccharinic acid; methanesulfonic acid; hydrobromic acid; hydrochloric acid; sulphuric acid; 1,2-ethanedisulfonic acid; (+/-)-camphorsulfonic acid; ethanesulfonic acid; nitric acid; p-xylenesulfonic acid; 2-mesitylenesulfonic acid; 1,5-naphthalenedisulfonic acid; 1-naphthalenesulfonic acid; 2-naphthalenesulfonic acid; benzenesulfonic acid; maleic acid; D-glutamic acid; L-glutamic acid; D,L-glutamic acid; L-arginine; glycine; salicylic acid; 10 tartaric acid; fumaric acid; citric acid; L-(-)-malic acid; D,L-malic acid and D-gluconic acid.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all tautomers, all stereo and optical isomers and racemates thereof as well 15 as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of 20 isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions, which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

25 Compounds of the present invention are intended to be chemically stable and it is assumed that it is within the skilled persons knowledge to identify which combinations of the above-defined groups in Formula I that may result in chemically unstable compounds of Formula 1.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight chain or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Specific compound of the invention includes:

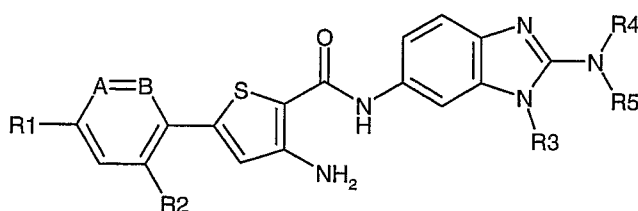
6-(4-Chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-one,

and tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I, in which X-Y represents N=N, may be prepared by reacting, at room temperature, a compound of formula II

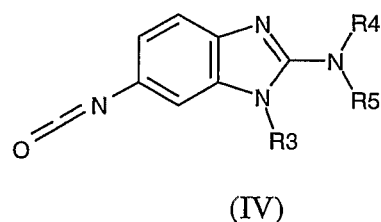
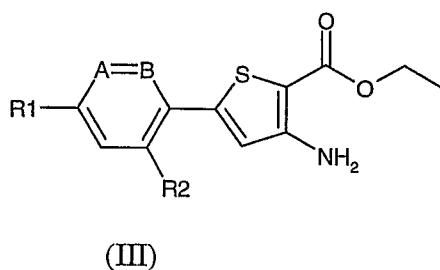


(II)

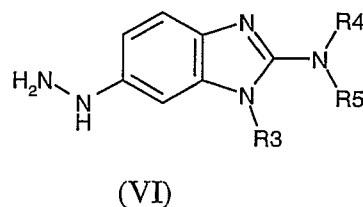
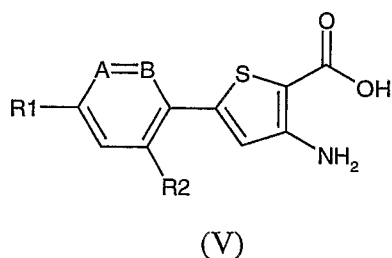
in which R^1 , R^2 , R^3 , R^4 , R^5 A and B are as previously defined, with a diazotizing agent such as sodium or potassium nitrite or t-butyl nitrite in a solvent or solvent mixture

containing acetic acid (75-100%) and water (0-25%), followed by alkaline aqueous work up, a method described e.g. in Daidone, G. et al. *Heterocycles* 43(11), 2385-96 (1996).

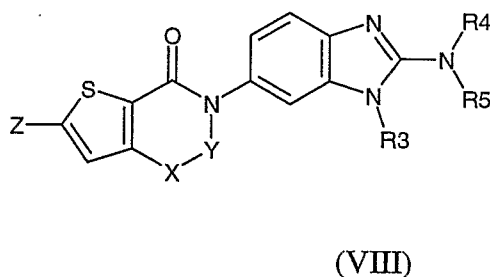
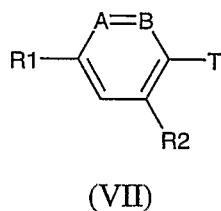
Compounds of formula I, in which X represents NH and Y represent C(O), may for example be prepared by reacting a compound of formula III with an aryl isocyanate IV, in analogy with methodology described in Graveleau, N. et al. *Synthesis* no 11, 1739-43 (2003).



Compounds of formula I, in which X-Y represent C=N, may for example be prepared by condensing, in refluxing EtOH followed by heating (of the intermediate hydrazone) in HOAc, a compound of formula V with an aryl hydrazine VI, in analogy with methodologies described in Baraldi, P.G. et al. *Nucleosides & Nucleotides* 17(12), 2165-73 (1998) and in Marquet, J-P. et al. *Tetrahedron* 29, 435-39 (1973)

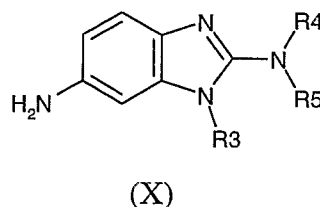
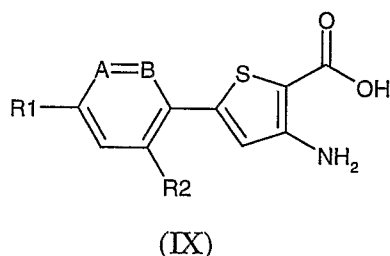


Alternatively, compounds of formula I may be prepared *via* a Suzuki or a Stille coupling reaction of a compound of formula VII with a compound of formula VIII



in which T represents $B(OH)_2$ or $Sn(alkyl)_3$ and Z represents a suitable leaving group such as I, Br or triflate.

Compounds of formula II may be prepared by coupling of compounds of formula IX with
5 compounds of formula X at a temperature in the range of $0^\circ C$ to $150^\circ C$, preferably in the range of $20^\circ C$ to $80^\circ C$ in the presence of a solvent, for example THF, DCM, NMP, DCM/water (i.e. a two phase system) or DMF, optionally in the presence of a suitable inorganic or organic base, e.g. DIPEA or TEA, and a standard amide coupling reagent, e.g. HATU, TBTU, TFFH, PyBroP, EDC, or DCC, the latter two of which may optionally be
10 polymer supported. Suitable additives such as HOBt and HOAt may optionally be used.



Persons skilled in the art will appreciate that in some cases, in order to obtain compounds
15 of the invention, functional groups in compounds II-X (e.g. hydroxy groups or amino groups in R^3 , R^4 or R^5 or carboxylic acids groups) may require protection prior to the reactions described above. Amine protecting groups are known to those skilled in the art, for example the benzyl, t-Boc, or Cbz groups. Aromatic amino groups may also be masked as nitro groups during the reaction sequence. Hydroxy protecting groups are known to
20 those skilled in the art, for example the t-butyl ether, TBDMS ether or THP, MEM or similar acetal type protecting groups. Carboxylic acid protecting groups are for example benzyl, t-butyl, ethyl or methyl esters.

Compounds of formulae II-X are either commercially available, known in the literature or
25 can readily be prepared by methods known to those skilled in the art.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques. Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. Enantiomers may be isolated by

separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (*i.e.* chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, or a pharmaceutically acceptable inorganic or organic addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-3 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5 mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg and 250 mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically

acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The compounds of the invention may also be combined with other therapeutic agents, which are useful in the treatment of disorders associated with obesity, psychiatric disorders, neurological disorders and pain.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, and diseases related to the respiratory and gastrointestinal systems. The compounds are also potentially useful as agents for ceasing consumption of tobacco, treating nicotine dependence and/or treating nicotine withdrawal symptoms, reducing the craving for nicotine and as anti-smoking agents. The compounds may also eliminate the increase in weight that normally accompanies the cessation of smoking. The compounds are also potentially useful as agents for treating or preventing diarrhea.

The compounds are also potentially useful as agents for reducing the craving/relapse for addictive substances that include, but are not limited to psychomotor-active agents such as nicotine, alcohol, cocaine, amphetamines, opiates, benzodiazepines and barbiturates. The compounds are also potentially useful as agents for treating drug addiction and/or drug abuse.

Accordingly, it is desirable to provide a compound and method of treatment which will be active in reducing craving for the abused substance, and which does not exacerbate the sympathetic response rate caused by the abused substance and which has favourable pharmacodynamic effects.

The compounds are also potentially useful as agents for treating pain disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine.

5

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particularly suitable for the treatment of obesity.

30

In another aspect the present invention provides a method of treating obesity, type II diabetes, Metabolic syndrome and a method of preventing type II diabetes comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

5 Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. For example, a compound of the present invention may be used in combination
10 with a compound that affects thermogenesis, lipolysis, fat absorption, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-
15 angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications; these include biguanide drugs, insulin (synthetic insulin analogues), oral antihyperglycemics (these are
20 divided into prandial glucose regulators and alpha-glucosidase inhibitors) and PPAR modulating agents.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in
25 association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-obesity compound, for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound, for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha

andadrenergic blocker, a beta andadrenergic blocker, a mixed alpha/beta andadrenergic blocker, an andadrenergic stimulant, calcium channel blocker, an AT-1 receptor blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist, for example rimonabant;

5 another melanin concentrating hormone receptor 1 (MCHr1) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

10 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for the
15 treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of
20 compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such
25 treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a
30 salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a

prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

5

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

10

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

15

20

Experimental section

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

25

Abbreviations:

Ac	acetyl
BSA	bovine serum albumin
Bu	butyl
t-Boc	<i>tert</i> -butyloxycarbonyl
CHO	Chinese hamster ovary (cells)

30

	DCM	methylene chloride, CH ₂ Cl ₂
	DIPEA	N,N-Diisopropylethylamine
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
5	DTT	dithiothreitol
	EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
	EDTA	ethylenediamine tetraacetic acid
	ELS	evaporative light scattering
	ESI	electrospray ionization
10	Et	ethyl
	GDP	guanosine 5'-diphosphate
	GPCR	G-protein coupled receptor
	GTP	guanosine triphosphate
	HATU	O-(azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluoro-
15		phosphate
	hERG	human <i>ether-a-go-go</i> related gene (potassium ion channel)
	HEPES	N-2-hydroxyethyl piperazine-N'-2-ethanesulfonic acid
	HPLC	high performance liquid chromatography
	HOAt	1-Hydroxy-7-azabenzotriazole
20	LC	liquid chromatography
	MS	mass spectroscopy
	PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
	TBTU	N, N, N', N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate
	TEA	triethylamine
25	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	Tris	trishydroxymethylaminomethane
	<i>t</i>	tert
	rt.	room temperature
30	sat.	saturated
	br	broad
	bs	broad singlet

d	doublet
dd	doublet of doublets
dt	doublet of triplets
m	multiplet
5 q	quartet
s	singlet
t	triplet

General Experimental Procedures

10 Flash column chromatography employed MERCK normal phase silica gel 60 Å (40-63 µm) or a Biotage Horizon Pioneer® HPFC system equipped with FLASH 12+M or FLASH 25+M or 40+M silica cartridges. Mass spectra were recorded on a Waters Micromass ZQ single quadrupole equipped with a pneumatically assisted electrospray interface (LC-MS).

15 HPLC analyses were performed on a Gynkotek P580 HPG, gradient pump with a Gynkotek UVD 170S UV-Vis detector. Column: Chromolith Performance RP-18e, 4.6 x 100 mm, Mobile phase A: Acetonitrile, Mobile phase B: 0.1% TFA (aq), Flow: 3 ml/min, Injection volume: 20 µl, Detection: 254 and 275 nm.

Purifications were performed on a semi preparative HPLC, Shimadzu LC-8A, Shimadzu
20 SPD-10A UV-vis. detector equipped with a Waters X-terra® Prep MS C₁₈ Column, 250 mm x 50 mm (10 µm) or on a Waters Prep LC 2000 with UV-detection, equipped with a Kromasil 10 µm C8 250 mm x 20 mm column, or on a semi preparative HPLC, Shimadzu LC-8A, Shimadzu SPD-10A UV-vis.-detector equipped with a Waters Symmetry® 100 mm x 19 mm C18 5 µm column.

25 ¹H NMR and ¹³C NMR spectra were obtained at 298 K on a Varian Unity Plus 400 MHz, or a Varian Inova 500 MHz or a Varian Unity Plus 600 MHz or a Bruker Avance 300 MHz or Varian Gemini 2000 300 MHz. Chemical shifts are given in ppm with the solvent residual peak as internal standard: CDCl₃ δ_H 7.26, δ_C 77.2; MeOH-*d*₄ δ_H 3.31, δ_C 49.0; DMSO-*d*₆ δ_H 2.50; δ_C 39.5 ppm.

30 Microwave heating was performed using single node heating in a Smith Creator from Personal Chemistry, Uppsala, Sweden.

Chemical names (IUPAC) were generated using the software ACD/ Name version 8.05. Names/reference numbers of starting materials (**CAS no**), either commercially available or prepared according to literature procedures.

- 5 methyl 3-amino-5-(4-chlorophenyl)thiophene-2-carboxylate, 91076-93-6
*N*²,*N*²,1-trimethyl-1*H*-benzimidazole-2,6-diamine, 462649-03-2

Working Example

10 **Example 1**

6-(4-Chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-one

a) 3-Amino-5-(4-chlorophenyl)thiophene-2-carboxylic acid

Methyl 3-amino-5-(4-chlorophenyl)thiophene-2-carboxylate (2.00 g, 7.47 mmol) was
15 refluxed in a solution of potassium hydroxide (2.0 g, 36 mmol) in 50 mL of water and 50 mL of methanol for 2 h. Methanol was evaporated and the residue was diluted to the double volume with water and washed with ethyl acetate. The aqueous layer was acidified with NaHSO₄ (aq) and the precipitate was filtered, washed with water and dried to give 1.85 g (98%) of the desired compound.

20 ¹H NMR (DMSO-*d*₆) δ 7.62 (m, 2H), 7.48 (m, 2H), 6.96 (s, 1H).

b) 3-Amino-5-(4-chlorophenyl)-*N*-[2-(dimethylamino)-1-methyl-1*H* benzimidazol-6-yl]thiophene-2-carboxamide

3-Amino-5-(4-chlorophenyl)thiophene-2-carboxylic acid (0.500 g, 1.97 mmol) was
25 dissolved in 10 mL of NMP. HATU (0.937 g, 2.46 mmol) and DIPEA (1.03 mL, 5.9 mmol) were added. The reaction was stirred overnight and *N*²,*N*²,1-trimethyl-1*H*-benzimidazole-2,6-diamine (0.375 g, 1.97 mmol) was added. The reaction mixture was heated to 80 °C for 1 h. The reaction mixture was poured into 200 mL of water and made alkaline with NaHCO₃ (aq). The mixture was extracted three times with ethyl acetate and
30 the combined organic layer was washed with water, dried over Na₂SO₄ and evaporated. The residue was flash chromatographed on silica gel with DCM/MeOH 9/1 to give 0.575 g (69%) of the desired compound.

¹H NMR (DMSO-d₆) δ 7.78 (s, 1H), 7.70 (d, 2H), 7.57 (d, 2H), 7.30 (m, 2H), 7.07 (s, 1H), 6.69 (s, 2H), 3.62 (s, 3H), 2.94 (s, 6H).

c) 6-(4-Chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*][1,2,3]triazin-4(3*H*)-one

3-Amino-5-(4-chlorophenyl)-*N*-[2-(dimethylamino)-1-methyl-1*H* benzimidazol-6-yl]thiophene-2-carboxamide (0.150 g, 0.352 mmol) was dissolved in 3 mL of acetic acid and 0.6 mL of water. Sodium nitrite (24 mg, 0.35 mmol) was added and the reaction was stirred for 10 min. The reaction mixture was poured into 50 mL of water and made alkaline with 1M NaOH and extracted three times with DCM. The combined organic layer was washed with water, dried over Na₂SO₄ and evaporated. The residue was recrystallised from DMSO to give the title compound. Yield: 60 mg (39%).

¹H NMR (CD₃COOD) δ 8.11 (s, 1H), 7.86 (d, 2H), 7.78 (s, 1H), 7.70-7.62 (m, 2H), 7.56 (d, 2H), 3.91 (s, 3H), 3.41 (s, 6H).

MS (ESI) 437/439 (M + 1H⁺).

Pharmacological Properties

MCHR1 radioligand binding.

Assays were performed on membranes prepared from CHO-K1 cells expressing the human Melanin concentrating hormone receptor 1 (hMCHR1, 5.45 pmol/mg protein; Euroscreen). Assays were performed in a 96-well plate format in a final reaction volume of 200 μl per well. Each well contained 6 μg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM MgCl₂, 0.05 % bovine serum albumin and the radioligand ¹²⁵I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per minute) per well. Each well contained 2 μl of the appropriate concentration of competitive antagonist prepared in DMSO or in HOAc and left to stand at 30 °C for 60 minutes. Non-specific binding was determined as that remaining following incubation with 1 μM MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a 1450 Microbeta TRILUX (Wallac, Finland).

Non-specific binding was subtracted from all values determined. Maximum binding was that determined in the absence of any competitor following subtraction of the value determined for non-specific binding. Binding of compounds at various concentrations was plotted according to the equation

5
$$y = A + ((B - A) / (1 + ((C/x)^D)))$$

and IC₅₀ estimated where

A is the bottom plateau of the curve i.e. the final minimum y value

B is the top of the plateau of the curve i.e. the final maximum y value

10 C is the x value at the middle of the curve. This represents the log EC₅₀ value when A + B = 100

D is the slope factor. x is the original known x values. y is the original known y values.

The compounds exemplified herein had an IC₅₀ of less than 100 nM in the abovementioned human MCHR1 binding assay. Preferred compounds had an activity of less than 20 nM. For instance, an IC₅₀ value of 2 nM was obtained for the compound of Example 1.

15 MCHR1 functional assay

Membranes expressing recombinant hMCHR1 (5.45 pmol/mg protein; Euroscreen) were prepared in assay buffer (50 mM HEPES, 100 mM NaCl, 5 mM MgCl₂, 1 mM EDTA, 200 μM DTT, 20 μM GDP (Sigma) containing 0.1 μg/ml BSA, pH7.4) before assay. The
20 assays were performed using membranes at 6 μg/well in an assay volume of 200 μL and the appropriate concentrations of compounds prepared in DMSO or in HOAc. The reaction was started by addition of 0.056 nM [³⁵S]GTPγS (Specific activity >1000 Ci/mmol; Amersham) and an ED₈₀ concentration of MCH (determined for each membrane and each MCH batch). Non-specific binding was determined using 20 μM non-radiolabelled GTPγS.
25 Plates were incubated for 45 min at 30°C. Free and bound GTPγS were separated by filtration binding using GF/B filter mats presoaked in wash buffer (50 mM Tris, 5 mM MgCl₂, 50 mM NaCl, pH 7.4) using a Micro96 cell harvester (Skatron Instruments) and the filters then dried at 50°C before counting using a 1450 Microbeta TRILUX (Wallac).

Data are means ± SD for experiments performed in triplicate. IC₅₀ values of antagonists
30 were determined using non-linear regression analysis of concentration response curves using Activity Base.

hERG activity

hERG testing was performed using a modified version of the method described by Kiss L, Bennett PB, Uebele VN, Koblan KS, Kane SA, Neagle B, Schroeder K. "High throughput ion-channel pharmacology: planar-array-based voltage clamp" *Assay Drug Dev Technol.* 1, 127-35. (2003). The compound of Example 1 had an IC₅₀ exceeding 5 μ M in the abovementioned assay.

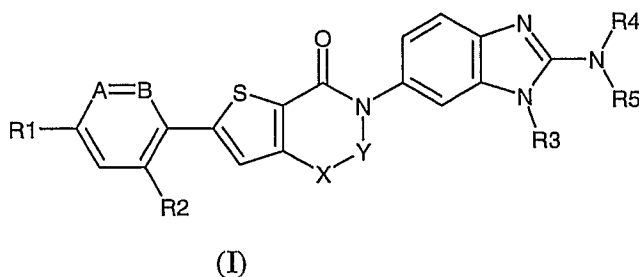
Diet induced obesity model in mouse

The utility of the compounds of the present invention in the treatment of obesity and related conditions is demonstrated by a decrease in body weight in cafeteria diet-induced obese mice. Female C57Bl/6J mice were given ad libitum access to calorie-dense 'cafeteria' diet (soft chocolate/cocoa-type pastry, chocolate, fatty cheese and nougat) and standard lab chow for 8-10 weeks until a body weight of 45-50 grams was achieved. Compounds to be tested were then administered systemically (iv, ip, sc or po) once daily for a minimum of 5 days, and the body weights of the mice monitored on a daily basis. During this period ad libitum access to calorie-dense 'cafeteria' diet and standard lab chow was maintained. Simultaneous assessment of adiposity was carried by means of DEXA imaging at baseline and termination of the study. Blood sampling was also carried out to assay changes in obesity-related plasma markers. Compounds of the invention induce significant decrease in body weight, with the major effect being via a reduction in fat-mass.

Compounds of the invention have the advantage that they may be more potent, more selective (e.g. vs. ion channels such as hERG and/or vs. GPCR's related to MCHR1) more efficacious in vivo, be less toxic, be longer acting, produce fewer side effects, be more easily absorbed, be less metabolised and/or have a better pharmacokinetic profile than, or have other useful pharmacological or physicochemical properties over, compounds known in the prior art.

Claims

1. A compound of formula I



wherein

A and B independently represent C or N,

X-Y represents C=N, or;

10 X represents NH and Y represents C=O, or;

X-Y represents N=N,

R¹ and R² independently represent H, C₁₋₃ alkyl (optionally substituted with one or more F), C₁₋₃ alkoxy (optionally substituted with one or more F), Cl or F,

15 R³ represents H, C₁₋₃ alkyl (optionally substituted with a hydroxy, methoxy, amino, methylamino, dimethylamino, pyrrolidinyl or morpholinyl group),

R⁴ and R⁵ independently represent H, C₁₋₃ alkyl (optionally substituted with a hydroxy, methoxy, amino, methylamino, dimethylamino, pyrrolidinyl or morpholinyl), or;

20 R⁴ and R⁵ are joined to form, together with the nitrogen atom to which they are attached, a pyrrolidine, piperidine, piperazine or morpholine ring (optionally substituted with hydroxy, oxo, C₁₋₃ alkyl (optionally substituted with hydroxy, methoxy or dimethylamino) or with a C₁₋₃ alkoxy group (optionally substituted with hydroxy, methoxy or dimethylamino)), and tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

25 2. A compound according to claim 1, in which

A and B both represent C, and

X-Y represents C=N, or

X-Y represents N=N.

3. A compound according to any of the preceding claims, in which
A and B both represent C, and
X-Y represents N=N.

5 4. A compound according to any of the preceding claims, in which
A and B both represent C,
X-Y represents N=N,

R¹ represents Cl, F, CF₃, CHF₂, CH₂F, methyl, OCF₃ or OCHF₂,

R² represents H, Cl, F or CH₃,

10 R³ represents methyl, ethyl, iso-propyl, hydroxyethyl or dimethylaminoethyl,

R⁴ and R⁵ independently represent H, methyl, hydroxyethyl or dimethylaminoethyl, or;

R⁴ and R⁵ are joined to form, together with the nitrogen atom to which they are attached, a
pyrrolidine, piperidine, piperazine or morpholine ring.

15 5. The compound:

6-(4-Chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-
d][1,2,3]triazin-4(3*H*)-one,

and tautomers, optical isomers and racemates thereof as well as pharmaceutically
acceptable salts thereof.

20 6. A compound of formula I as claimed in any one of claims 1 to 5 for use as a
medicament.

7. A pharmaceutical formulation comprising a compound of formula I, as defined in any
25 one of claims 1 to 5 and a pharmaceutically acceptable adjuvant, diluent or carrier.

8. Use of a compound of formula I as defined in any one of claims 1 to 5 in the
preparation of a medicament for the treatment or prophylaxis of conditions associated with
obesity.

30 9. A compound as defined in any one of claims 1 to 5 for use in the treatment of obesity.

10. A method of treating obesity, psychiatric disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders and pain related disorders, comprising administering a pharmacologically effective amount of a compound
5 as claimed in any one of claims 1 to 5 to a patient in need thereof.

11. A method of treating obesity, type II diabetes, metabolic syndrome and prevention of type II diabetes comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 5 to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2006/000879

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004092181 A1 (SMITHKLINE BEECHAM CORPORATION), 28 October 2004 (28.10.2004), claim 1, example 11 -- -----	1-11

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 October 2006

Date of mailing of the international search report

27-10-2006

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International patent classification (IPC)

C07D 495/04 (2006.01)
A61K 31/5025 (2006.01)
A61K 31/519 (2006.01)
A61K 31/53 (2006.01)
A61P 03/04 (2006.01)
A61P 25/00 (2006.01)

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000879

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-11
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 10-11 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been for these claims, based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/10/2006

International application No. -

PCT/SE2006/000879

WO	2004092181	A1	28/10/2004	CA	2521832	A	28/10/2004
				EP	1618112	A	25/01/2006
				MX	PA05010859	A	14/12/2005
				US	20060194871	A	31/08/2006
